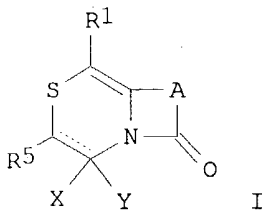
L6 ANSWER 1 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:888746 HCAPLUS
DOCUMENT NUMBER: 138:4599
TITLE: Preparation of fused imidazolidine derivatives as inhibitors of **cartilage** matrix degradation
INVENTOR(S): Funabashi, Yasunori; Takizawa, Masayuki; Morimoto, Shinji; Notoya, Kohei
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 940 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2002092606 | A1 | 20021121 | WO 2002-JP4640 | 20020514 |
| WO 2002092606 | C1 | 20021219 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG | | | | |
| JP 2003034691 | A2 | 20030207 | JP 2002-139642 | 20020515 |

PRIORITY APPLN. INFO.: JP 2001-144608 A 20010515
OTHER SOURCE(S): MARPAT 138:4599
GI



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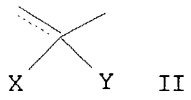

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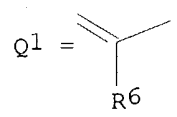
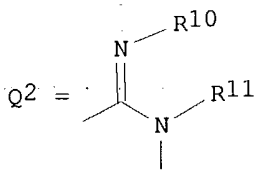



AB The title compds. I [R1 = (S)nR2, etc.; n = 0 - 2; R2 = H, (un)substituted

hydrocarbon, etc.; R5 = H, (un)substituted hydrocarbon, etc.; the moiety represented by II in I is Q1, etc.; R6 = H, (un)substituted hydrocarbon, etc.; A = Q2, etc.; R10 = H, ZR15, etc.; Z = SO2, etc.; R15 = (un)substituted hydrocarbon, etc.; R11 = H, (un)substituted hydrocarbon] are prepared A process for preparing I is disclosed. Compds. of this invention in vitro at 0.1 μM gave 20% to 55% inhibition of MMP-13 production Formulations are given.

REFERENCE COUNT: 22 THERE ARE 22 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:490169 HCAPLUS
DOCUMENT NUMBER: 137:277009
TITLE: Effect of **proteoglycan** on experimental colitis
AUTHOR(S): Majima, Mitsuo; Takagaki, Keiichi; Sudo, Shin-ichiro; Yoshihara, Syuichi; Kudo, Yoshiaki; Yamagishi, Shohei
CORPORATE SOURCE: Kakuhiro Co. Ltd., Aomori, 030-8543, Japan
SOURCE: International Congress Series (2001), 1223(New Developments in Glycomedicine), 221-224
CODEN: EXMDA4; ISSN: 0531-5131
PUBLISHER: Elsevier Science B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of **proteoglycan** (PG) on colitis was examined in animal expts. using mice. The PG used was extracted from nasal **cartilage** of salmon head with 4% **acetic acid** and prepared by precipitation with ethanol followed by dialysis. The PG contained about 7% protein, and had a mol. mass of 344 kDa on SDS/PAGE. The glycosaminoglycan (GAG) sugar chains of the PG were composed of hexosamine, uronic acid and sulfate at a molar ratio of 1.0:1.0:0.7. The mice were divided into a control group and an administration group. The control group was given free access to drinking water containing dextran sulfate sodium salt (DSS) to induce colitis. On the other hand, the administration group was given free access to drinking water containing DSS and PG. Then, the time course of survival rates in both groups were measured. In the administration group, the survival rate increased significantly in comparison with that of the control group. The difference in the survival rates indicated that the onset of mouse colitis induced by DSS was inhibited by administration of the PG.

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2002:157148 HCAPLUS
DOCUMENT NUMBER: 136:163703
TITLE: A method for extraction and purification of **cartilage** type **proteoglycan**
INVENTOR(S): Takagaki, Keeichi
PATENT ASSIGNEE(S): Kakuhiro Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 8 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| EP 1182209 | A2 | 20020227 | EP 2001-117771 | 20010801 |
| EP 1182209 | A3 | 20030205 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| JP 2002069097 | A2 | 20020308 | JP 2000-251071 | 20000822 |
| US 2002045735 | A1 | 20020418 | US 2001-916250 | 20010730 |
| CN 1439663 | A | 20030903 | CN 2002-104684 | 20020220 |

PRIORITY APPLN. INFO.: JP 2000-251071 A 20000822

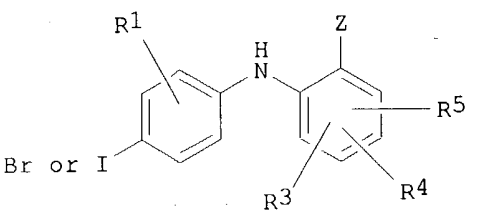
AB The present invention relates to a new method for extraction and purification of **cartilage** type **proteoglycan**, and is to provide a method for extraction of crude **proteoglycan** characterized by the use of acid as eluting solvent of **cartilage**.

L6 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:420949 HCAPLUS
DOCUMENT NUMBER: 133:73860
TITLE: Preparation of 2-(4-bromo or 4-iodo phenylamino)benzoic acid derivatives as MEK inhibitors
INVENTOR(S): Dudley, David Thomas; Flory, Craig Mason; Saltiel, Alan Robert
PATENT ASSIGNEE(S): Warner-Lambert Company, USA
SOURCE: PCT Int. Appl., 106 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000035436 | A2 | 20000622 | WO 1999-US29783 | 19991215 |
| WO 2000035436 | A3 | 20011018 | | |
| W: AE, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| CA 2346448 | AA | 20000622 | CA 1999-2346448 | 19991215 |
| EP 1143957 | A2 | 20011017 | EP 1999-966278 | 19991215 |
| EP 1143957 | A3 | 20020227 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |

PRIORITY APPLN. INFO.: US 1998-112544P P 19981216
US 1999-164651P P 19991110
WO 1999-US29783 W 19991215

OTHER SOURCE(S): MARPAT 133:73860
GI

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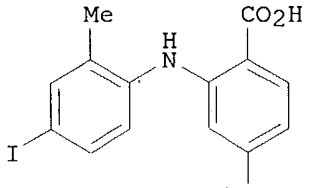


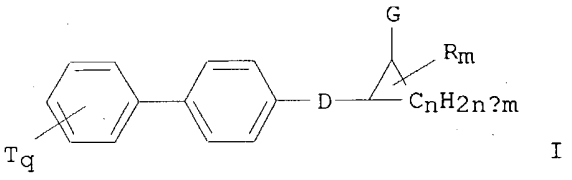

II

AB The title compds. (I) [wherein R1 = H, OH, alkyl, alkoxy, halo, CF3, or CN; R3-R5 = independently H, OH, halo, CF3, alkyl, alkoxy, NO2, CN, or (O or NH)m-(CH2)n-R9, where R9 = H, OH, CO2H, or NR10R11; m = 0 or 1; n = 0-4; R10 and R11 = H, alkyl, or taken together with the N to which they are attached form a 3-10 membered ring; Z = CO2R7, tetrazolyl, CONR6R7, CONHNR10R11, or CH2OR7; R6 and R7 = independently H, (cyclo)alkyl, alkenyl, alkynyl, acyl, (hetero)aryl, or taken together with the N to which they are attached form a 3-10 membered ring, etc.] were prepared by standard or combinatorial synthetic methods involving the addition of halobenzoic acids to haloanilines and optional reduction or amidation of the acid. For example, treatment of 2-amino-5-iodotoluene in THF with LDA in THF/heptane/ethenylbenzene solution, followed by addition of 2,4-difluorobenzoic acid in THF afforded II. In assays against type II collagen induced arthritis in mice and monoarticular arthritis in rats, I showed potent anti-arthritic activity. I inhibited IL-1 induced stromelysin production in rabbit synovial fibroblast cell cultures with IC50 from 9 nM to 192 nM. Interleukin 1-alpha stimulated **cartilage** degradation was reduced by up to 75% in New Zealand white rabbits upon administration of I. Thus, I are potent MEK inhibitors useful in the prevention and treatment of rheumatoid arthritis or osteoarthritis.

L6 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1999:205318 HCAPLUS
DOCUMENT NUMBER: 130:267212
TITLE: Biphenyl-derived substituted cycloalkanecarboxylic acid derivatives and analogs as matrix metalloprotease inhibitors
INVENTOR(S): Kluender, Harold Clinton Eugene; Bullock, William Harrison; Dixon, Brian Richard; Schneider, Stephan; Vanzandt, Michael Christopher; Wilhelm, Scott McClelland; Wolanin, Donald John
PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: U.S., 102 pp., Cont. of U.S. Ser. No. 463,471, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5886022 | A | 19990323 | US 1997-866568 | 19970530 |
| PRIORITY APPLN. INFO.: | | | US 1995-463471 | 19950605 |

OTHER SOURCE(S): MARPAT 130:267212
GI

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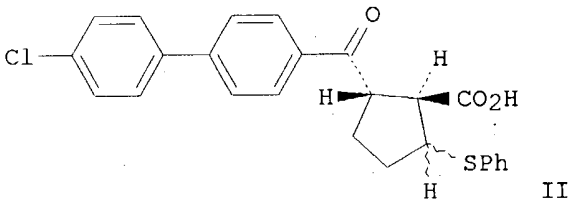


II

AB The invention discloses inhibitors for matrix metalloproteases (MMPs), pharmaceutical compns. containing the inhibitors, and a process for using them to treat a variety of physiol. conditions. The claimed compds. have the generalized formula I [wherein each T = halo, alk(en/yn)yl, (CH2)pQ, etc.; Q = aryl, heteroaryl, cyano, CHO, NO2, etc.; p = 0-4; q = 0-2; D = CO, CH(OH), C:NOH, C:S; n = 2 or 3; R = alk(en/yn)yl, aralk(en/yn)yl; G = CO2H, alkoxycarbonyl, (di)(alkyl)carbamoyl, or amino acid residues bound at N via a CO linker; m = 0-2]. Approx. 250 compds. including both I and many acyclic carboxylic acid analogs were prepared For instance, Friedel-Crafts acylation of 4-chlorobiphenyl by 1-cyclopentene-1,2-dicarboxylic anhydride, followed by lithiation/reprotonation to effect double-bond isomerization, and Michael addition of thiophenol to the double bond, gave 2 diastereomers of title compound II. The trans,trans isomer of II was the most active diastereomer, with IC50 values as follows: MMP-3 14-47 nM, MMP-9 56 nM, and MMP-2 4 nM.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 6 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:742237 HCAPLUS
DOCUMENT NUMBER: 130:17266
TITLE: Chemical cleaning of biological material
INVENTOR(S): Abraham, Ginger A.; Carr, Robert M., Jr.; Kemp, Paul D.; Mercer, Ryan; Baker, Linda
PATENT ASSIGNEE(S): Organogenesis Inc., USA
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9849969 | A1 | 19981112 | WO 1998-US9432 | 19980508 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| US 5993844 | A | 19991130 | US 1997-853372 | 19970508 |
| AU 9872947 | A1 | 19981127 | AU 1998-72947 | 19980508 |
| AU 736312 | B2 | 20010726 | | |
| BR 9809216 | A | 20000627 | BR 1998-9216 | 19980508 |
| EP 1018979 | A1 | 20000719 | EP 1998-920349 | 19980508 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| JP 2002510995 | T2 | 20020409 | JP 1998-548536 | 19980508 |
| NO 9905372 | A | 19991103 | NO 1999-5372 | 19991103 |
| MX 9910251 | A | 20000630 | MX 1999-10251 | 19991108 |
| US 6599690 | B1 | 20030729 | US 1999-450577 | 19991130 |
| US 2004005703 | A1 | 20040108 | US 2003-615623 | 20030708 |

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|---|---|---|---|
| PRIORITY APPLN. INFO.: | US 1997-853372 | A2 | 19970508 |
| | WO 1998-US9432 | W | 19980508 |
| | US 1999-450577 | A1 | 19991130 |

AB Collagenous tissues are treated to remove noncollagenous components such as cells, cellular debris, and other extracellular matrix components such as **proteoglycans** and glycosaminoglycans, normally found in native tissues, by treatment of the tissue with alkali, chelating agents, acids, and salts while controlling the amount of swelling and dissoln. so that the resultant collagen matrix retains its structural organization, integrity, and bioremodelable properties. The process circumvents the need to use detergents and enzymes, which detrimentally affect the cell compatibility, strength, and bioremodelability of the collagen matrix. The collagenous tissue matrix is used for implantation, repair, or similar use in a mammalian host. Thus, pig small intestine was mech. stripped to remove fat, muscle, and mucosal layers from the tunica submucosa. The submucosa was then shaken successively at .apprx.200 rpm with (a) 100 mM tetra-Na EDTA/10 mM NaOH for 18 h, (b) 1M HCl/1M NaCl for 6-8 h, (c) 1M NaCl/10 mM phosphate-buffered saline for 18 h, (d) 10 mM phosphate-buffered saline for 2 h, and (e) sterilized water for 1 h. Treated tissue samples appeared free of cells and cellular debris.

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 7 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN

ACCESSION NUMBER: 1998:534889 HCAPLUS

DOCUMENT NUMBER: 129:161412

TITLE: Derivatives of substituted 4-biarylbutyric acid as matrix metalloprotease inhibitors

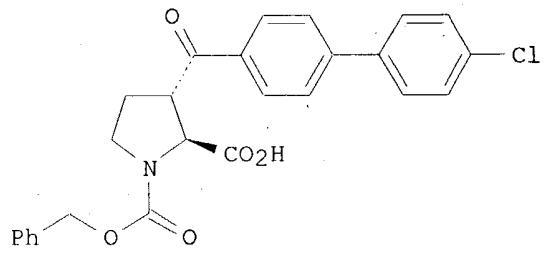
INVENTOR(S): Kluender, Harold Clinton Eugene; Benz, Guenter Hans Heinz Herbert; Brittelli, David Ross; Bullock, William Harrison; Combs, Kerry Jeanne; Dixon, Brian Richard; Schneider, Stephan; Wood, Jill Elizabeth; Vanzandt, Michael Christopher; Wolanin, Donald John; Wilhelm, Scott M.

PATENT ASSIGNEE(S): Bayer Corporation, USA
SOURCE: U.S., 109 pp., Cont.-in-part of U.S. Ser. No. 339,846.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5789434 | A | 19980804 | US 1995-539409 | 19951106 |
| CA 2201863 | AA | 19960523 | CA 1995-2201863 | 19951109 |
| CN 1163604 | A | 19971029 | CN 1995-196209 | 19951109 |
| CN 1121376 | B | 20030917 | | |
| HU 78083 | A2 | 19990830 | HU 1998-233 | 19951109 |
| PT 790974 | T | 20021129 | PT 1995-940572 | 19951109 |
| ES 2181803 | T3 | 20030301 | ES 1995-940572 | 19951109 |
| ZA 9509647 | A | 19970814 | ZA 1995-9647 | 19951114 |
| TW 413675 | B | 20001201 | TW 1995-84112045 | 19951114 |
| US 5874473 | A | 19990223 | US 1997-864666 | 19970528 |
| US 5886024 | A | 19990323 | US 1997-865325 | 19970528 |
| US 5854277 | A | 19981229 | US 1997-865639 | 19970530 |
| US 5859047 | A | 19990112 | US 1997-866798 | 19970530 |
| US 5861427 | A | 19990119 | US 1997-866679 | 19970530 |
| US 5861428 | A | 19990119 | US 1997-866680 | 19970530 |
| US 5886043 | A | 19990323 | US 1997-866778 | 19970530 |
| US 6166082 | A | 20001226 | US 1998-57679 | 19980409 |

PRIORITY APPLN. INFO.:
US 1994-339846 A2 19941115
US 1995-462729 B1 19950605
US 1995-463490 B1 19950605
US 1995-463580 B1 19950605
US 1995-463794 B1 19950605
US 1995-464253 B1 19950605
US 1995-465626 B1 19950605
US 1995-539409 A 19951106

OTHER SOURCE(S): MARPAT 129:161412
GI




I

AB Matrix metalloprotease (MMP) inhibitors TxA-B-D-E-G [I; T = halo, haloalkyl, alkynyl, (un)substituted alkyl or alkenyl; x = 0, 1, 2; A, B = aromatic or heteroarom. ring; D = CO, CH(OH), CH2, C:NOH, C(S); E = substituted carbon chain; G = PO3H2, CO2H, CO2NH2, 5-tetrazolyl, etc.] and their pharmaceutically acceptable salts were prepared In particular, I [A = C6H4; B = 1,4-C6H4; E = certain substituted THF, tetrahydrothiophene, or

pyrrolidine divalent radicals] with MMP inhibitory activity, and their pharmaceutically acceptable salts, are claimed. For instance, claimed title compound II was prepared from L-pyroglutaminol in 9 steps. The synthesized compds. (444) were assayed for inhibition of MMP-3, MMP-9, and MMP-2. For instance, II had corresponding IC50 values of 103, 381, and 35 nM. I inhibited tumor growth and metastasis in animal models, and inhibited **cartilage** lesions in a guinea pig model of osteoarthritis.

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1997:702288 HCAPLUS
DOCUMENT NUMBER: 127:329857
TITLE: Reaction of hypochlorous acid with bovine nasal **cartilage** comparison to pig articular **cartilage**
AUTHOR(S): Schiller, Jurgen; Arnhold, Jurgen; Zachaus, Annett; Arnold, Klaus
CORPORATE SOURCE: Medizinische Fakultat, Universitat Leipzig, Leipzig, D-04103, Germany
SOURCE: Zeitschrift fuer Naturforschung, C: Biosciences (1997), 52(9/10), 694-701
CODEN: ZNCBDA; ISSN: 0341-0382
PUBLISHER: Verlag der Zeitschrift fuer Naturforschung
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The action of NaOCl on bovine nasal **cartilage** was studied by 1H-NMR spectroscopy to model degradation processes of **cartilage** caused by neutrophil-derived hypochlorous acid. Nasal **cartilage** was chosen as a mean of comparison because it differs from articular **cartilage** in its composition It contains some more **proteoglycans**, i.e. polymeric carbohydrates and less collagen than articular **cartilage**. This is important for studying the influence of hypochlorous acid on **cartilage** components (collagen and polysaccharides). **Cartilage** samples were incubated at 37° with phosphate buffer in the presence or absence of NaOCl. Supernatants were collected and assayed by NMR-spectroscopy. In the presence of pure phosphate buffer, the supernatants of bovine nasal **cartilage** were less rich in low mol. mass metabolites (e.g. amino acids, lactate) than articular **cartilage**. However, intense signals for highly mobile N acetyl groups of **cartilage** polysaccharides were detectable in nasal **cartilage**. NaOCl caused an increase in signals for acetate and formate. Signals for N-acetyl groups rose only during the 1rst 25 min of incubation with NaOCl. Then, their concentration decreased markedly. These changes were related to an enhanced release of chondroitinsulfate from nasal **cartilage**.

L6 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1996:476807 HCAPLUS
DOCUMENT NUMBER: 125:142275
TITLE: Substituted 4-biarylbutyric or 5-biarylpentanoic acids and derivatives as matrix metalloprotease inhibitors
INVENTOR(S): Kluender, Harold Clinton Eugene; Benz, Guenter Hans Heinz Herbert; Brittelli, David Ross; Bullock, William Harrison; Combs, Kerry Jeanne; Dixon, Brian Richard; Schneider, Stephan; Wood, Jill Elizabeth; Vanzandt,

Michael Christopher; et al.
PATENT ASSIGNEE(S): Bayer A.-G., USA
SOURCE: PCT Int. Appl., 263 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9615096 | A1 | 19960523 | WO 1995-US14002 | 19951109 |
| W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
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| EP 790974 | B1 | 20020814 | | |
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OTHER SOURCE(S): MARPAT 125:142275

AB Matrix metalloprotease inhibitors TxA-B-D-E-G [Tx = substituent such as halo, C1-C10 alkyl, or cyanoalkenyl; x = 0, 1, 2; A, B = aromatic or

heteroarom. ring; D = CO, CH(OH), CH2, C:NOH, C(S); E = substituted carbon chain; G = PO3H2, CO2H, CO2NH2, etc.] and their pharmaceutically acceptable salts were prepared Thus, (S)-γ-oxo-4'-(pentyloxy)-α-(3-phenylpropyl)-[1,1'-biphenyl]-4-butanoic acid (86) was prepared via alkylation of di-Et (3-phenylpropyl)malonate with 2,4'-dibromoacetophenone, followed by saponification-monodecarboxylation, reaction with 4-methoxybenzeneboronic acid, Me ether cleavage, and O-pentylation. The synthesized compds. (444) were assayed for inhibition of MMP-3, MMP-9, and MMP-2. Using compds. such as 86, the number of tumor metastases was decreased between 38 and 49% as compared to the control. The title compds. were also assayed for inhibition of **cartilage** lesions in a guinea pig model of osteoarthritis.

L6 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1989:209947 HCAPLUS
DOCUMENT NUMBER: 110:209947
TITLE: Effects of chondroitinase-ABC on **proteoglycans** and swelling properties of fibrocartilage in bovine flexor tendon
AUTHOR(S): Koob, Thomas J.
CORPORATE SOURCE: Dep. Biol., Univ. New Mexico, Albuquerque, NM, 87131, USA
SOURCE: Journal of Orthopaedic Research (1989), 7(2), 219-27
CODEN: JOREDR; ISSN: 0736-0266
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Fibrocartilaginous regions of bovine deep flexor tendon were treated with chondroitinase-ABC and trypsin to extract **proteoglycans** from the extracellular matrix and thereby investigate the contribution of **proteoglycan** and collagen organization to tissue material properties. Chondroitinase-ABC digestion of tendon specimens for 24 h resulted in extraction of 60% of the tissue glycosaminoglycans and leaching of the degraded large **proteoglycan** from the tissue residue. The totally degraded core protein of the small dermatan sulfate **proteoglycan** remained with the tissue residue, indicating that it is specifically associated with the tissue residue and that this association is not dependent on the glycosaminoglycan chains. Treatment of residues with trypsin after chondroitinase-ABC digestion depleted the specimens of **proteoglycan**. Bulk swelling tests on enzyme-extracted specimens showed that the distinct swelling properties of the fibrocartilaginous regions of the distal flexor tendon could be partially accounted for by elevated levels of **proteoglycan**. Swelling tests also showed that the distinct collagen organization of this region contributes significantly to the tissue's material properties. Apparently, the fibrocartilaginous organization and composition of the articulating layer of distal tendon are adapted for mech. requirements unique to this site, which receives compressive and frictional loads in addition to tensile loads.

L6 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1973:54498 HCAPLUS
DOCUMENT NUMBER: 78:54498
TITLE: Structural studies on **cartilage** collagen employing limited cleavage and solubilization with pepsin
AUTHOR(S): Miller, Edward J.
CORPORATE SOURCE: Med. Cent., Univ. Alabama, Birmingham, AL, USA

SOURCE: Biochemistry (1972), 11(26), 4903-9
CODEN: BICHAW; ISSN: 0006-2960
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Insol. **cartilage** collagen was prepared as the residue from the sternal **cartilages** of 10-week-old chickens by exhaustive extraction with M NaCl at neutral pH and 0.5 M **acetic acid**. The extraction procedures were totally ineffective in solubilizing **cartilage** collagen but were useful as a means of removing **proteoglycan** components of the tissue. Amino acid analyses of the insol. **cartilage** collagen residue revealed an amino acid composition closely resembling that of purified α1(II) chains. Characterization of the CNBr cleavage products derived from insol. **cartilage** collagen indicated that they are, for the most part, qual. identical with those previously observed in CNBr digest of α1(II) prepared from soluble **cartilage** collagen. However, 2 addnl. CNBr peptides (designated peptides 14 and 15) comprising a total sequence of 21 amino acids derived from a nonhelical region of the **cartilage** collagen mol. were identified. Incubation of insol. **cartilage** collagen in 0.5 M **acetic acid** containing pepsin (ratio of collagen: enzyme = 10:1) at 4° for 18 hr solubilized 60-70% of the collagen. Characterization of the pepsin-solubilized **cartilage** collagen with respect to chain composition, mol. weight of the component α chains and CNBr cleavage products of the chains indicated that the collagen was solubilized as monomeric mols. of the chain composition, {α1(II)}3, and that the proteolytic activity of pepsin on the native **cartilage** collagen mol. is confined to relatively short sequences represented by the CNBr peptides, 1,4,14,15, and the CO2H-terminal portion of peptide 7. These results indicating that the cited sequences do not participate in collagen helix formation and that they are localized at the extremities of the α1(II) chains comprising the **cartilage** collagen mol. have been used, in conjunction with addnl. data on the location of peptides 1 and 4, to establish that the order of the CNBr peptides in the carboxy-terminal region of the α1(II) chain is: 7-14-15. These results further indicate that failure to detect peptides 14 and 15 in the CNBr cleavage products of α1(II) prepared from soluble **cartilage** collagen resulted from nonspecific proteolytic activity during extraction and purification of the collagen. It is proposed that the mechanism whereby the proteolytic activity of pepsin alters the solubility properties of **cartilage** collagen involves, at least in part, the degradation of the sequence represented by peptide 4, thus effectively eliminating a site of intermol. cross-linking known to occur in this sequence.